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The Brain-Gut Connection and the Autistic Spectrum Disorder

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Abstract: ***The autism spectrum disorder (ASD) occurs in one out of every 68 individuals and can affect any child regardless of sex, race or socioeconomic status. This study enrolled all patients with the diagnosis of ASD attended the Unit of Gastroenterology, Food Allergy and Autism at the Unigranrio University. All of these patients were investigated for food allergy (FA). The gastrointestinal tract of patients with ASD has been extensively studied in recent decades and reveals indistinguishable findings from those found in FA. It is observed that autism often establishes itself as a disease in patients with adequate psychomotor development and without previous neurological conditions, but with FA preceding the neurological deficits. We hypothesized that FA is one of the foregoing factors in patients who develop ASD, if they suffer from inflammation of the central nervous system (CNS). This inflammatory injury may turn neurons the target organ or the FA homing site, once the brain-gut connection is established by different mechanisms.***

Keywords: brain-gut connection, GALT disease, food allergy and ASD, neurons inflammation, CNS immune target organ

1. Introduction

Autism spectrum disorder (ASD) is characterized by disorders of the neurological development, typically diagnosed in the first 4 years of life, which presents clinically with compromised social interaction, deficits in verbal and non-verbal communication and stereotypes behaviors with repetitive non-purposive finality.(1-3) Occurs in one in 68 individuals and can affect any child regardless of gender, race or socioeconomic condition, being four to five times more frequent in sex masculine. (4)

In the literature indexed so far, ASD does not have a defined etiology and the pathophysiological mechanisms involved remain unknown. Current studies in search of these mechanisms and etiopathogenesis investigated the genetic, environmental and immunization causes. For this shortage of information on ASD, its treatment takes unpredictable and being a fallacy.(5) The lack of understanding about the disease is particularly of worse, because of the increase in prevalence, since ASD has already at epidemics levels.(6)

By studying patients with food allergy (FA) it is possible to observe that genetic factors, environmental factors and immunizations are also present in different moments, in expressive numbers. Genetic predisposition, which in this case determines the ability to respond with allergy to non-pathogens antigens, is fundamental to the genesis of allergic disease and also is present in the ASD. Children of both allergic parents have 80% of chance to be allergic and we observed that in more than 85% of the patients with ASD, there was a family history of respiratory and food allergies.(7)

Since 1998, with our publication of a prior notice in "The Lancet" signaling that patients with FA presented endoscopic alterations and in the biopsies of the terminal ileus shown similar aspects to those described in patients with ASD (8,9), we start extensively research in the link of FA and ASD. Surprisingly we found that 100% of the patients with ASD were diagnosed also with FA, being the GI tract, more specifically the GALT system (gastrointestinal associated lymphoid tissue), the mucosal-associated lymphoid tissue (MALT) of higher prevalence of involvement before the onset of the neurological disturbance that makes up the development of ASD.

2. Material and Methods

We included in this study all patients with previous diagnosis of ASD, attended at the outpatient clinic Unit of Gastroenterology, Food Allergy and Autism of the University Unigranrio (UGAAA). The diagnosis of FA was made through the Score for the Diagnosis of FA (10), through physical examination focused on the identification of clinical multisystemic involvement and with the laboratory investigation that identifies the immune mediation present in each patients with ASD and FA.

We collect information by reviewing the medical records, characterizing this study as a retrospective cross-sectional study. Some figures do not present the same total of patients, because over the years, we added new data to the anamnesis, according to the progress of the literature in this area. The UNIGRANRIO Ethics and Research Committee approved this research project under number CAAE 66813917.0.0000.5283. The Free and Informed Consent Term is in accordance with resolution number 466 of December 12, 2012, of National Health Council, on research involving human beings.

3. Results

A total of 86 patients previously diagnosed within the spectrum of of autism were studied and in 100% of these ASD patients the diagnosis of FA was present in 100% of then. In order to identify which of the two pathologies, ASD or FA, was established first in each individual, the number of MALTs affected before the start of the ASD was measured. Only two of the 86 ASD patients studied did not contain this information, belonging to a study conducted 20 years ago. It is clear that FA is a pre-existing condition, since that 98.8% patients had at least one MALT affected before the onset of ASD ,(Figure 1) and only one patient (1.2%) enters in the spectrum of ASD involvement at the same time of interrupting breastfeeding.

In 84%, there was GALT involvement preceding ASD (Figure 2), others lymphoid tissues were also affected previously, but not so expressively. Immune mediations varied, 34% had mixed mediation, secondly with 32% the mediation was Th2, followed by 23% who presented Th1 mediation and 11% with other immune mediations such as NK cells involvement.

4. Discussion

Food allergy is a multifactorial disease that develops in the presence of factors such as inadequate breastfeeding, the health of the mother and her GI tract disease, during pregnancy and breastfeeding, complications and sterile (cesarean) deliveries and early exposure to cow's milk and, to a lesser extent, wheat and soybean (11). Once sensitized to a particular antigen, the individual may respond with food allergy in case that this conjuncture of factors is present. After immune activation in the Peyer patches (PP) of the GALT system, the antigens, lymphocytes and inmunoglobulins, continue to search for their “homing” clinical response. The "homing" chosen may be in the BALT (bronchial associated lymphoid tissue), the NALT (nasal associated lymphoid tissue), in the SALT (skin associated lymphoid tissue), or can come back to GALT itself or go to the CNSALT (central nervous system associated lymphoid tissue), involved in ASD. The definition of which body system will be affected is influenced by the genetic inheritance, environmental factors and other inflammatory factors that function as triggers for the involvement of lymphoid tissues. (12-14)

Inflammation, physical and psychic trauma, infections and vaccine with neurotrophic agents (mainly measles, sabin and pertussis) has the potential to directly the inflammation to the neurons and make the central nervous system (CNS) the homing for the immune system affected in FA , attracting the circulating lymphocytes and the immunoglobulins that participate in the process of FA, to the CNS. (5) The clinical manifestations of the aggression to the CNS can thus cause the individual to develop the autism spectrum, varying clinically according to the affected area and the degree of allergic aggression to the CNS.

In addition to sharing the same embryonic ectodermal origin, the CNS, the Skin and GI tract are connected by about 3,000 neurons. The number is few but expressive, when compared to the 100 million neurons that make up the intestinal nerve plexus. (14) This abundance of neurons in the presence of FA, a condition that generates inflammation, favors homing to local neurons, causing alteration in peristalsis of the gastrointestinal tract , and probably for the CNS as well. It is often observed constipation, as a pattern of bowel movements in ASD. But those with the disorder have various forms of dysmotility other than diarrhea and constipation, (5,15-18), often misinterpreted as behavioral issues (19-22)

There is concrete evidence of immune activation in ASD, which is the finding of nodular lymphoid hyperplasia in the ileal-colonic area (INLH). (8) Since 1998, it has been described the association between ASD and this activation of peyer's patches (PP). This fact corroborates the finding of FA throughout all of this population.

One of the most important signal of FA with GALT involvement is the dysmotility, secondary to gastroparesis, that can be presenting as gastroesophageal reflux in the newborn or dyspepsia in older children, such as in schoolchildren the verification of gastric emptying time with Tc99 we are able to diagnosis and assess the dysmotility. (23-25) The change in peristalsis found in ASD patients occurs due to defective transmission of the nerve impulse, due to defects transmission between the neurons of the intestinal plexuses and the smooth muscle, probably due to the inflammation capable of altering the physiology of the neural cell.(26,27)

The GALT system was the most affected MALT (84%) preceding the onset of neurodevelopmental disorders that composed of ASD. (28-48) This fact supports the hypothesis of inflammation in the enteric nervous system favor the homing for both local neurons and the neurons of the CNS, since the lymphatic pathway has recently been recognized by immunological surveillance of both. (17) The inflammatory process from FA has continued exposure to antigens of the diet against which patients react on both GI tract and CNS, thus evolving into GALT and CNSALT disease. The interruption of this exposure, with the restrictive diet for FA antigens, is therefore justified, causing inflammation to cease in these systems affected. (16)

In October 2015, in the journal Nature, the brain-gut connection goes into because a growing set of data, mostly in mice, demonstrates that the intestinal microbiota influences behavior and can change the physiology of the brain and neurochemistry. (49,50) However, it follows the question whether the microbial differences associated with diseases are causes or only consequences. It is postulated that there is more speculation than data to date. Also in mice, it was possible to shown that the metabolites produced by their microbiota are capable of to change the blood-brain barrier, such as butyrate (short fatty acid) approaching the intercellular junctions of the barrier. (43)

Recent studies have shown that the cerebellum, besides participating in the motor coordination, it also plays an important role in the motor, cognition and emotional processes. (51) Motor abnormalities, cognitive and emotional problems, may result from damage to portions of

the cerebellum projecting to motor areas, prefrontal cortex and limbic, respectively. (52,53) There is also evidence that the cerebellum is related to various cognitive abnormalities and psychopathological manifestations. (54-57)There is a strong association between abnormalities in the cerebellum and psychiatric illnesses such as schizophrenia, bipolar disorder, depression, anxiety disorders, ADHD and ASD. (58-71) It should be noted that there is a strong association between allergic diseases (allergic rhinitis, atopic eczema and asthma) with ADHD and that other psychiatric disorders such as anxiety disorder disorder, obsessive-compulsive disorder and Tourette's syndrome are also found more frequently in atopic patients. (72-77). Currently, three cerebellar abnormalities are recognized in patients with ASD: (71) decreased number of Purkinje cells, cerebellar volume reduction and interruption of feedback between the cerebellar pathway and the cortex. The cells of Purkinje are of an inhibitory nature and their lack would diminish the inhibition that the cerebellum projects in the cortical and subcortical areas, leading to hypersensitivity of these regions in the brain found in most patients with ASD. (78-81)

In 2002, it was reported in Neurology that gliadin proteins and the cells of Purkinje of the cerebellum share common epitopes. (78). In some patients with ASD have already been identified antibody against cells of Purkinje and against the peptides of gliadin, which may be related to the genesis or the exacerbation of autism. (79) Probably there is this reactivity between gluten and Purkinje cells, although the antigliadin antibodies are not the only ones that react with the epitopes of these cells. The Immunohistochemistry demonstrates that the removal of antibodies against gliadin of the patients serum does not brake all the reactivity to the epitopes of the Purkinje cells. In patients with Gluten Ataxia, in addition to anti-gliadin, we have oligoclonal bands in the cerebrospinal fluid, inflammation in the cerebellum and Purkinje anti-cell antibodies. (80)

In view of the fact that anti-gliadin withdrawal does not origin in the cerebellum, the arbitrary withdrawal of gluten from the diet of all patients with ASD, who usually present with this inflammation, are not justified. We therefore stress the need for FA in order to understand the type of immune response involved and which allergens that are participating in the aggression.

5. Conclusion

The brain-gut connection is established in several ways, from indirectly through the microbiota and the metabolites that it produces even directly as the gluten-Purkinje molecular mimicry or the homing for the enteric and CNS neurons. The clinical manifestations of AA in the CNS can thus cause the individual to enter the spectrum of autism, varying clinically according to the affected area and the degree of allergic aggression.

Some conducts can be adopted prophylactically to avoid establishment of FA (82-87), and if the patient develops FA, we should avoid GI disease and concomitant CNS aggression, cause of inflammation in these systems. The protection of neurons will be through the restrictive diet, which ceases inflammation in these affected systems, until the resolution of FA, digestive disease and the consequent aggression to the SNC. (88)

References

[1] Amaral DG, Schumann CM, Nordahl CW Neuroanatomy of autism. Trends Neurosci. 2008; 31: 137–45 doi: 10.1016/j.tins.2007.12.00518258309
[2] Acosta MT, Pearl PL The neurobiology of autism: new pieces of the puzzle. Curr Neurol Neurosci Rep. 2003; 3: 149–56 12583844
[3] Geschwind, D.H. Advances in autism. Annu. Rev. Med. 2009, 60, 367–380.
[4] "Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010." Centers for Disease Control and Prevention, 28 Mar 2014. Web 25 May 2015.
[5] Sabra A, Tenório I, Sabra S. Manual de Alergia Alimentar, 3 Ed., 2015, Editora Rubio, Rio de Janeiro, Rj.
[6] Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, et al. (2011) Prevalence of autism spectrum disorders in a total population sample. Am J Psychiat 168: 904–912.
[7] Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. The Lancet. 1998;351(9103):637–641.
[8] Sabra A, Bellanti J, Colon A. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. The Lancet 08/1998; 352(9123):234-5.
[9] González L, López C, Navarro D, Negrón L, Flores L, Rodríguez R, Martínez M, Sabrá A, Caracteristicas Endoscópicas, Histologicas e Inmunologicas de la Mucosa Digestiva en Niños Autistas con Síntomas Gastro-Intestinales, Archivos Venezolanos de Puericultura y Pediatría 2006; Vol 69
[10]. Sabra A, Tenorio I, Sabra S. Score for the diagnosis of food allergy. Journal of Food Allergy, 2012. Vol. 01 (2): 173-180.
[11] Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ, Gastrointestinal factors in autistic disorder: a critical review. J Autism Dev Disord. 2005;35(6):713–727
[12] McElhanon BO, McCracken C, Karpen S, Sharp WG,Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis, Pediatrics 2014 133:872-883
[13] Buie T, Campbell DB, Fuchs GJ III, Sabra A, et al, Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010; 125(suppl 1): S1–S18
[14] Huquet G, Ey E, Bourgeron T. The genetic landscapes of autism spectrum disorders. Annu Re Genomics Hum Genet. 2013; 14: 191-213.
[15] Sabra A, Corsini L, Tenorio I, Sabra S, Nemer JM, Sabra Filho A. Food allergy and autistic spectrum disorder. Journal of Food Allergy, 2015. Vol. 04 (1): 4-17.
[16] Sabra A, Bellanti JA, Zeligs BJ. Gastrointestinal immunopathology and food allergy. Ann Allergy Asthma Immunol. 2004. 93: 26-32.

[17] Louveau, Antoine. Structural and Functional Features of Central Nervous System Lymphatic Vessels. Nature. 2015; Jul 16,523(7560):337-41.
[18] Ransohoff, R. M. & Engelhardt, B. The anatomical and cellular basis of immune surveillance in the central nervous system. Nature Rev Immunol. 2012; 12, 623–635.
[19] Kipnis, J., Gadani, S. & Derecki, N. C. Pro-cognitive properties of T cells. Nature Rev. Immunol. 2012; 12: 663–669.
[20] Shechter, R., London, A. & Schwartz, M. Orchestrated leukocyte recruitment to immune-privileged sites: absolute barriers versus educational gates. Nature Rev. Immunol. 2013; 13: 206–218.
[21] Sabra A, Bellanti JA, Castro HJ, Chavez JR, Malka-Rais J, Inocencio JM. Are attention deficit hyperactivity disorder and chronic fatigue syndrome related? What is fibromyalgia? Allergy Asthma Proc, Georgetown University Medical. 2005; 26(1): 19-28.
[22] Gershon MD. The enteric nervous system: a second brain. Hospital Practice. 1999; 34(7): 31–42.
[23] Pang KH, Croaker GD.. Constipation in children with autism and autistic spectrum disorder. Pediatr Surg Int. 2011; 27: 353–8.
[24] White JF.. Intestinal pathophysiology in autism. Exp Biol Med (Maywood). 2003; 228: 639–49.
[25] Buie T, Fuchs GJ, III, Furuta GT, Kooros K, Levy J, Sabra A, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics. 2010; 125: S19–29.
[26] Verhoeven WM, Egger JI, Cohen-Snuijf R, Kant SG, de Leeuw N. Phelan-McDermid syndrome: clinical report of a 70-year-old woman. Am J Med Genet A. 2013; 161A: 158–61.
[27] Chaudhury, A. Molecular Handoffs in Nitrergic Neurotransmission. Frontiers in Medicine. 2014; 8: PMC. Web. 2 Nov. 2015.
[28] Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G.. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry. 2008; 47: 921–9.
[29] Dalrymple NJ, Ruble LA. Toilet training and behaviors of people with autism: parent views. J Autism Dev Disord. 1992; 22: 265–75.
[30] Matson JL. Simple correction for treating an autistic boy's encopresis. Psychol Rep. 1977; 41:802-10.
[31] Galiatsatos P, Gologan A, Lamoureux E. Autistic enterocolitis: Fact or fiction? Canadian Journal of Gastroenterology. 2009; 23(2): 95-98.
[32] Wakefield AJ, Ashwood P, Limb K, Anthony A. The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. European Journal of Gastroenterology and Hepatology. 2005; 17(8): 827–836.
[33] Wasilewska J., Jarocka-Cyrta E., Kaczmarski M. Gastrointestinal abnormalities in children with autism. Pol. Merkur. Lekarski. 2009; 27: 40–43.
[34] Sabra A, Corsini L, Tenorio I, Sabra S, Nemer JM, Sabra Filho A. The brain-intestine connection and the autistic spectrum disorder. Journal of Food Allergy. 2015; Vol. 04 Suppl (1): 18-26.
[35] Sabra A, Corsini L, Tenorio I, Sabra S, Nemer JM, Sabra Filho A. Alergia alimentar, agressão imune ao sistema nervoso central e novas fronteiras no tratamento do transtorno do espectro autista. Pediatria Moderna. 2016; Jan 16 V 52 N 1: 452-467.
[36] Phelan MC, Stapleton GA, Rogers RC. The Management of Genetic Syndromes. Hoboken: Wiley-Liss, Ed. (2010).
[37] Betalli P, Carretto E, Cananzi M, Zanatta L, Salvador R, Galeazzi F, et al. Autism and esophageal achalasia in childhood: a possible correlation? Report on three cases. Dis Esophagus. 2013; 26: 237–40.
[38] Chaidez V, Hansen RL, Hertz-Picciotto I.. Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord. 2013; 43; 803-13
[39] Carroccio A, Iacono G. Review article: Chronic constipation and food hypersensitivity–an intriguing relationship. Aliment Pharmacol Ther. 2006; 6(9): 1295–1304.
[40] Peeters B, Noens I, Philips EM, Kuppens S, Benninga MA.. Autism spectrum disorders in children with functional defecation disorders. J Pediatr; 2013: 163: 873–8.
[41] Chandler S, Carcani-Rathwell I, Charman T, Pickles A, Loucas T, Meldrum D, et al. Parent-reported gastro-intestinal symptoms in children with autism spectrum disorders. J Autism Dev Disord. 2013; 43: 2737–47.
[42] Furuta GT, Williams K, Kooros K, Kaul A, Panzer R, Coury DL, et al. Management of constipation in children and adolescents with autism spectrum disorders. Pediatrics. 2012; 130: S98–105.
[43] Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA.. Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. Dig Dis Sci. 2012; 57: 2096–102.
[44] Wang LW, Tancredi DJ, Thomas DW.. The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. J Dev Behav Pediatr. 2011; 32: 351–60.
[45] Pang KH, Croaker GD.. Constipation in children with autism and autistic spectrum disorder. Pediatr Surg Int. 2011; 27: 353–8.
[46] Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ.. Gastrointestinal factors in autistic disorder: a critical review. J Autism Dev Disord. 2005; 35: 713–27.
[47] Parkman HP, Miller MA, Fisher RS. Role of nuclear medicine in evaluating patients with suspected gastrointestinal motility disorders. Semin Nucl Med. 1995; 25(4): 289–305.
[48] Won H, Mah W, Kim E.. Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. Front Mol Neurosci. 2013; 6: 19-29.
[49] Smith PA, The tantalizing links between gut microbes and the brain. Nature News. 2015; (15;526) (7573): 312-4.
[50] Braniste, Viorica et al. The Gut Microbiota Influences Blood-Brain Barrier Permeability in Mice. Sci Transl Med. 2014; 6: 263-68.

[51] Phillips Joseph, Hewedi Doaa Hamed, Eissa Abeer, Moustafa Ahmed A. The cerebellum and psychiatric disorders. Frontiers in Public Health. 2015; vol. 3.
[52] Manto M, Oulad Ben Taib N. The contributions of the cerebellum in sensorimotor control: what are the prevailing opinions which will guide forthcoming studies? Cerebellum. 2013; 12(3): 313–5.
[53] Stoodley CJ. The cerebellum and cognition: evidence from functional imaging studies. Cerebellum. 2012; 11(2): 352–65.
[54] Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum – insights from the clinic. Cerebellum. 2007; 6(3): 254–67.
[55] Marien P, Wackenier P, De Surgeloose D, De Deyn PP, Verhoeven J. Developmental coordination disorder: disruption of the cerebello-cerebral network evidenced by SPECT. Cerebellum. 2010; 9(3): 405–10.
[56] Chen YL, Tu PC, Lee YC, Chen YS, Li CT, Su TP. Resting-state fMRI mapping of cerebellar functional dysconnections involving multiple large-scale networks in patients with schizophrenia. Schizophr Res. 2013; 149(1–3): 26–34.
[57] Fatemi SH, Folsom TD, Rooney RJ, Thuras PD. Expression of GABAA alpha2-, beta1- and epsilon-receptors are altered significantly in the lateral cerebellum of subjects with schizophrenia, major depression and bipolar disorder. Transl Psychiatry. 2013; 3: 303-38.
[58] Baldacara L, Nery-Fernandes F, Rocha M, Quarantini LC, Rocha GG, Guimaraes JL, et al. Is cerebellar volume related to bipolar disorder? J Affect Disord. 2011; 135(1–3): 305–9.
[59] Liang MJ, Zhou Q, Yang KR, Yang XL, Fang J, Chen WL, et al. Identify changes of brain regional homogeneity in bipolar disorder and unipolar depression using resting-state FMRI. PLoS One. 2013; 8(12): 79999.
[60] Bledsoe JC, Semrud-Clikeman M, Pliszka SR. Neuroanatomical and neuropsychological correlates of the cerebellum in children with attention-deficit/hyperactivity disorder – combined type. J Am Acad Child Adolesc Psychiatry. 2011; 50(6): 593–601.
[61] Liu L, Zeng LL, Li Y, Ma Q, Li B, Shen H, et al. Altered cerebellar functional connectivity with intrinsic connectivity networks in adults with major depressive disorder. PLoS One. 2012; 7(6): 39516.
[62] Ma Q, Zeng LL, Shen H, Liu L, Hu D. Altered cerebellar-cerebral resting-state functional connectivity reliably identifies major depressive disorder. Brain Res. 2013; 1495: 86–94.
[63] Peng J, Liu J, Nie B, Li Y, Shan B, Wang G, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: a voxel-based morphometry study. Eur J Radiol. 2011; 80(2): 395–9.
[64] Nakao T, Sanematsu H, Yoshiura T, Togao O, Murayama K, Tomita M, et al. fMRI of patients with social anxiety disorder during a social situation task. Neurosci Res. 2011; 69(1): 67–72.
[65] Schutter DJ, Koolschijn PC, Peper JS, Crone EA. The cerebellum link to neuroticism: a volumetric MRI association study in healthy volunteers. PLoS One. 2012; 7(5): 37252.
[66] Talati A, Pantazatos SP, Schneier FR, Weissman MM, Hirsch J. Gray matter abnormalities in social anxiety disorder: primary, replication, and specificity studies. Biol Psychiatry. 2013; 73(1): 75–84.
[67] An L, Cao QJ, Sui MQ, Sun L, Zou QH, Zang YF, et al. Local synchronization and amplitude of the fluctuation of spontaneous brain activity in attention-deficit/hyperactivity disorder: a resting-state fMRI study. Neurosci Bull. 2013; 29(5): 603–13.
[68] Tomasi D, Volkow ND. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012; 71(5): 43–50.
[69] Wang X, Jiao Y, Tang T, Wang H, Lu Z. Altered regional homogeneity patterns in adults with attention-deficit hyperactivity disorder. Eur J Radiol. 2013; 82(9): 1552–7.
[70] Marko MK, Crocetti D, Hulst T, Donchin O, Shadmehr R, Mostofsky SH. Behavioral and neural basis of anomalous motor learning in children with autism. Brain. 2015; 138(Pt 3): 784-97.
[71] Wegiel J, Flory M, Kuchna I, Nowicki K, Ma S, Imaki H, et al. Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. Acta Neuropathol Commun. 2014; 2(1): 141-7.
[72] Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attentiondeficit/hyperactivity disorder? A systematic review. Allergy. 2010; 65:1506-1524.
[73] Shyu CS, Lin HK, Lin CH, et al. Prevalence of attention-deficit/hyperactivity disorder in patients with pediatric allergic disorders: a nationwide, population-based study. J Microbiol Immunol Infect. 2012; 45: 237-242.
[74] Yuce M, Guner SN, Karabekiroglu K, et al. Association of Tourette syndrome and obsessive-compulsive disorder with allergic diseases in children and adolescents: a preliminary study. Eur Rev Med Pharmacol Sci. 2014; 18: 303-310.
[75] Chen MH, Su TP, Chen YS, et al. Is atopy in early childhood a risk factor for ADHD and ASD? a longitudinal study. J Psychosom Res. 2014; 77: 316-321.
[76] Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics. 2007; 120(3): 584–93.
[77] Baron-Cohen S, Ashwin E, Ashwin C, Tavassoli T, Chakrabarti B. Talent in autism: hyper-systemizing, hyper-attention to detail and sensory hypersensitivity. Philos Trans R Soc Lond B Biol Sci. 2009; 364(1522): 1377–83.
[78] Hadjivassiliou M, Boscolo S, Davies-Jones GA, Grunewald RA, Not T, Sanders DS, et al. The humoral response in the pathogenesis of gluten ataxia. Neurology. 2002; 58: 1221–1226.
[79] Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and Psychiatric Manifestations of

Celiac Disease and Gluten Sensitivity. The Psychiatric quarterly. 2012; 83(1): 91-102.
[80] Sander HW, Magda P, Chin RL, Wu A, Brannagan TH, 3rd, Green PH, et al. Cerebellar ataxia and coeliac disease. Lancet. 2003; 362: 1548.
[81] Burk K, Melms A, Schulz JB, Dichgans J. Effectiveness of intravenous immunoglobin therapy in cerebellar ataxia associated with gluten sensitivity. Annals of Neurology. 2001; 50: 827–828.
[82] Kawicka A., Regulska-Ilow B. How nutritional status, diet and dietary supplements can affect autism. A review. Rocz. Panstw. Zakl. Hig. 2013; 64: 1–12.
[83] Schultz ST, Klonoff-Cohen HS, Wingard DL, et AL, . Breastfeeding, infant formula supplementation, and autistic disorder: the results of a parent survey. Int Breastfeed J. 2006; 1: 16
[84] Martín R, Heilig GH, Zoetendal EG, Smidt H, Rodríguez JM. Diversity of theLactobacillus group in breast milk and vagina of healthy women and potential role in the colonization of the infant gut. J Appl Microbiol. 2007; 103(6): 2638–2644.
[85] Critchfield JW, van Hemert S, Ash M, Mulder L, Ashwood P, The potential role of probiotics in the management of childhood autism spectrum disorders. Gastroenterol Res Pract. 2011; 2011: 161358.
[86] Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism: comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 2011; 11: 22.
[87] Parracho HM, Bingham MO, Gibson GR, McCartney AL, Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol. 2005; 54(pt 10): 987-991.
[88] Sabra A, Corsini L, Tenorio I, Sabra S, Nemer JM, Sabra Filho A. The brain-intestine connection and the autistic spectrum disorder. Journal of Food Allergy. 2015; Vol. 04 (1): 18-26.

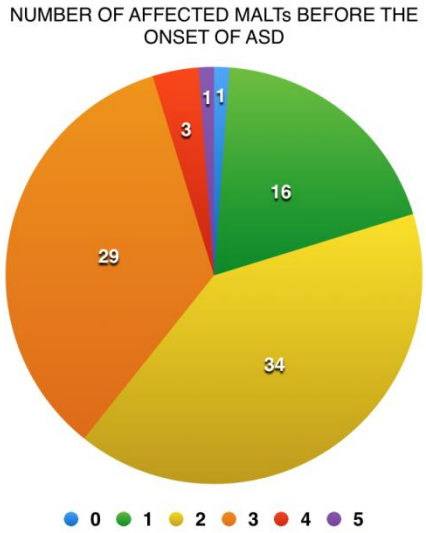

Figure 1: Number of MALTs affected before the onset of ASD

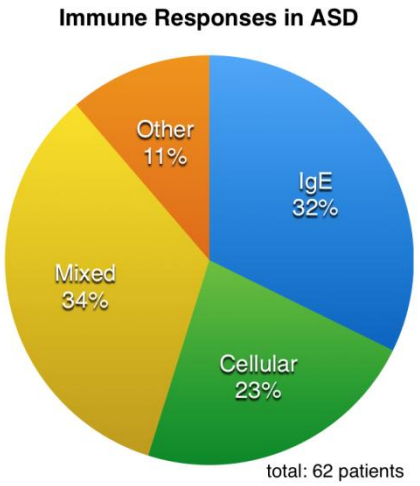

Figure 2: Immune mediation in 62 patients with ASD and FA